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EXAMINER	
MYERS, CARLA J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,664	LENZ ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2008 and 15 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7-11 and 16-33* is/are pending in the application.

4a) Of the above claim(s) *7-11 and 29-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 16-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/15/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed May 14, 2008. Applicant's arguments have been fully considered but are not persuasive to place all claims in condition for allowance.

All rejections not reiterated herein are hereby withdrawn. In particular, the objections over claims 2-6 and 12 have been obviated by the amendments to the claims. The rejections of claims 1-6 and 12-15 under 35 U.S.C. 112, second paragraph have been obviated by the amendments to the claims. The rejection of claims 1-6 and 12-15 under 35 U.S.C. 112, first paragraph, written description, has been obviated by the amendment to the claims to recite the genotype at codon 118 of the ERCC1 gene, and particularly the C/C, T/C and T/T genotypes at codon 118 of the ERCC1 gene. The provisional obviousness-type double patenting rejections of claims 1-4, 12 and 15 over copending Application Nos. 09/715,764, 11/681,670 and 11/681,695 have been obviated by the amendment to the claims. The rejection of claims 1-6 and 12-15 under 35 U.S.C. 102(b) as being anticipated by Yu et al. has been obviated by the amendment to the claims to recite that the method is one for treating metastatic colorectal cancer and to recite "wherein the patient is selected for treatment with said therapy based on the presence of the genotype C/C."

The paper and CRF copies of the Sequence Listing filed on May 14, 2008 have been entered.

This action contains new grounds of rejection necessitated by Applicant's amendments to the claims and is made final.

Election/Restrictions

2. Claims 1, 4, 7-11, and 16-33 are pending.

Claims 7-11 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on September 9, 2007.

In the reply of May 14, 2008, Applicant added new claims 16-33. In the reply, Applicants state that "All of the above claims are within the elected invention of group I." However, claims 29-33 are drawn to an invention non-elected without traverse in the response of September 9, 2007. In particular, these claims are directed to the subject matter of methods of treatment by administering the fluropyrimidine 5-FU (i.e., a COX-2 inhibitor) and a platinum drug. This is the subject matter of non-elected Group II (see, for example, non-elected claim 9). It is noted that claims 29-33 recite the limitation of a "patient selected for said therapy based on the possession of the genotype C/C at codon 118 of the ERCC1 gene." However, the claims do not recite an active process step of selecting a patient for therapy by assaying for the presence of the C/C genotype at codon 118 of the ERCC1 gene. Therefore, this recitation does not limit the claim to methods of selecting therapy by assaying for the genotype at codon 118 of the ERCC1 gene, which is the subject matter of elected group I. The claims also encompass treating any patient with the stated therapy since the claims state that the patient is treated based on the possession of the C/C genotype, and thereby may be selected based on the presence or absence of the possession of the C/C genotype. Accordingly,

claims 29-33 are directed to the subject matter of non-elected Group II and are withdrawn from consideration.

Therefore, claims 1, 4 and 16-28 have been examined herein. Claims 7-11 and 29-33 are withdrawn from consideration as being drawn to a non-elected invention.

Maintained Rejections

Claim Rejections - 35 USC § 112 - Enablement

3. Claims 1, 4 and 16-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for predicting the survival of a human patient having metastatic colon cancer, the method comprising: i) obtaining a nucleic acid sample from colon cancer tissue or colon cancer cells of a human patient having metastatic colon cancer and treated with 5-fluorpyrmidine (5-FU) and oxaliplatin, wherein the nucleic acid sample comprises ERCC1 nucleic acids; ii) analyzing the sequence of the ERCC1 nucleic acids to determine the nucleotides present at codon 118; and iii) determining that the patient will have a longer survival following treatment with 5-FU and oxaliplatin if the patient has a C/C genotype at codon 118 of ERCC1, as compared to patients having a C/T or T/T genotype at codon 118 of ERCC1, does not reasonably provide enablement for methods which select any therapeutic regimen in any subject having any type of cancer by assaying for any polymorphism or genotype of the ERCC1 gene or any other gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection was previously presented in the Office action of November 14, 2007 and has been modified below to address the amendments to the claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 1, 4, and 16-18 as amended are drawn to methods for selecting a therapy comprising a fluoropyrimidine and a platinum drug to treat metastatic colorectal cancer comprising screening a cell or tissue sample isolated from said patient for the genotype at codon 118 of the ERCC1 gene, wherein the patient is selected for treatment with said therapy based on the presence of the genotype C/C. Claims 19-28 are drawn to methods for determining whether a patient with metastatic colorectal cancer is likely to experience longer survival following treatment with a fluoropyrimidine and a platinum drug comprising screening a cell or tissue sample isolated from said patient for the genotype at codon 118 of the ERCC1 gene, wherein the presence of the genotype C/C is indicative that the patient is more likely to have a longer survival following treatment and the genotypes C/T or T/T are indicative that the patient is less likely to experience longer survival following said treatment.

Claims 1, 4, 16, 17, 19-21, 23-26 and 28 encompass selecting a therapy with any type of a fluoropyrimidine drug and/or platinum drug.

The claims do not recite the methodology by which the genotype at codon 118 is determined. Thereby, the claims encompass methods of indirectly detecting the genotype, including methods which assay for a change in ERCC1 mRNA levels as indicative of the genotype at codon 118.The claims also include assaying any type of biological sample.

Nature of the Invention

The claims are drawn to methods for methods for selecting a therapeutic regimen by screening a patient sample for a genotype. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

With respect to the elected invention of the ERCC1 gene, the specification discloses only one polymorphism in the human ERCC1 gene – i.e., a C to T substitution at codon 118, which does not alter the amino acid sequence of the ERCC1 protein (see page 35). The specification further teaches the results of a genotyping study of intratumor tissues obtained from 60 metastatic colon cancer patients that received 5-FU/oxaliplatin chemotherapy (pages 34-36). It is stated that patients with the C/C genotype had a median survival of 531 days, whereas the median survival for patients with the C/T and T/T genotypes was 254 days and 256 days, respectively (page 36).

Regarding the prior art, the specification (page 35) teaches:

> Studies have shown that increased ERCC1 mRNA levels are directly related to clinical resistance to cisplatin in human ovarian cancer as well as cervical cancer. It has previously been shown that ERCC1 mRNA levels are also directly correlated to clinical resistance to 5-FU and cisplatin in gastric cancer patients. It has also recently been shown that intra-tumoral ERCC1 mRNA levels are able to predict clinical response and overall survival in patients with metastatic colorectal cancer treated with 5- FU/oxaliplatin.

The specification (page 35) also teaches that the presence of the T/T and T/C genotypes are correlated with higher levels of ERCC1 mRNA. It is stated that the median ERCC1 mRNA level is 2.95, and that 27.3% of patients with the C/C genotype had mRNA levels greater than 2.95, whereas 41.7% and 77.8% of patients with the C/T and T/T genotype had mRNA levels greater than 2.95. Thus, the specification (page 35) concludes that When the mRNA levels of patients containing the C allele was compared to those without the C allele, the difference was statistically significant ($p=0.049$).

The Predictability or Unpredictability of the Art :

The specification (page 35) identifies only one polymorphism in the human ERCC1 gene (the C to T substitution at codon 118 of exon 4) and states that the C/C genotype is correlated with increased survival in metastatic colon cancer patients treated with 5-FU/oxaliplatin. The art of determining an association between a genotype and a phenotype is highly unpredictable. Knowledge that a polymorphism exists does not allow one to conclude that the polymorphism is associated with a phenotype, such as response to treatment. Further, knowledge that a polymorphism is associated with one phenotype, effective response following 5-FU/oxaliplatin treatment, does not allow

one to conclude which, if any, additional phenotypes (effective response to other chemotherapeutic agents) will also be associated with the presence of the polymorphism or combination of polymorphisms.

In particular, it is highly unpredictable as to what would be the identity of additional polymorphisms in the ERCC1 gene or in other unspecified genes that could be used to select a therapeutic regimen to treat cancer. The genus of genes, and polymorphisms in genes, that may be correlated with any type of response to any chemotherapeutic agent is incredibly large. The specification does not disclose a representative number of these polymorphisms or genotypes that could be used to select a therapeutic regimen.

The unpredictability of establishing an association between a polymorphism and a phenotype is well accepted in the art. For example, Hirschhorn et al. (Genetics in Medicine. 2002. 4(2): 45-61) teaches that most reported associations between genetic variants and phenotypes are not robust. Hirschhorn states that "of the 166 putative associations studied three or more times, only 6 have been consistently replicated" (see abstract). The reference sets forth a number of reasons for the irreproducibility of these studies, suggesting that population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn concludes that "the current irreproducibility of most studies should raise a loud cautionary alarm" (page 60, col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The unpredictability of identifying additional variants of ERCC1 correlated with response to treatment is supported by the post-filing date art of Winter (Oncogene. 2005. 24: 2110-2113). Winter discloses a mutation in exon 1 of ERCC1, resulting in a differentially spliced variant of ERCC1. It is stated that this variant has been previously disclosed as being associated with ERCC1 mRNA levels (page 2110). However, Winter found that the variant and wildtype ERCC1 transcripts were present at similar ratios in the tissues examined. Winter (page 2111) states that this data does not support the conclusion that the polymorphism leading to the alternatively spliced transcript is associated with ERCC1 mRNA levels. Winter (page 211s) also teaches that the alternatively spliced transcript is present in both normal and cancer cells and does not appear to be related to the occurrence of cancer.

It is also highly unpredictable as to whether the results obtained with survival of metastatic colon cancer patients following 5-FU/oxiplatin treatment can be extrapolated to other treatment regimens and other types of outcomes.

The unpredictability of extrapolating the results obtained with the codon 118 polymorphism to other types of outcomes and responses to other chemotherapeutic agents is emphasized by the teachings of Yu et al. (Mutation Research. 1997. 382: 13-20). Yu (Table 2 and page 19) found that the 118 AAT and AAC codons were present in both ovarian cancer tissues that were sensitive to cisplatin treatment and in ovarian cancer tissues that were resistant to cisplatin treatment. Yu did not observe an association between the occurrence of the C/C, C/T or T/T genotypes and response to cisplatin in ovarian cancer patients. This unpredictability is also supported by the

teachings of Lee (Proceedings American Association Cancer Research. 2005. 46: Abstract 1496) wherein it is disclosed that expression levels of ERCC1 are not correlated with survival following cisplatin-based adjuvant therapy in resected gastric cancer.

The teachings of Kang (Experimental and Molecular Medicine. 2006. 38: 320-324) also emphasizes the unpredictability in the art, particularly with respect to extrapolating the findings obtained with the codon 118 polymorphism and response to other types of treatment in other types of cancers. Kang reports that the C/T and T/T genotypes were correlated with reduced risk of platinum-resistance in ovarian cancer. However, no significant association was observed between the ERCC1 polymorphism and overall survival in ovarian cancer patients treated with platinum-based drugs (see abstract and page 323). Further, Kang states that, as of 2006, the mechanism by which the ERCC1 polymorphism effects response to chemotherapy remains unclear. It is stated that "functional data supporting the association between the ERCC1 polymorphism and its activity are still controversial and insufficient" (page 323).

The unpredictability of extrapolating the results obtained with the codon 118 polymorphism to response to other chemotherapies is also supported by the post-filing date art of Viguier (Clinical Cancer Research. 2005. 11: 6212-6217). Viguier teaches that while the codon 118 T/T genotype was associated with response of metastatic colorectal cancer patients to 5-FU/oxiplatin, the T/T, C/T and C/C genotypes were not associated with response to 5-FU alone or 5-FU in combination with irinotecan (page 6215). The reference (page 6216) teaches that the lack of association between the

ERCC1 polymorphism and response to 5-FU therapy "is not surprising because ERCC1 is unlikely to play a role in the repair of 5-FU-induced lesions." Moreover, Viguier (page 6216) teaches the unpredictability of indirectly assaying for the codon 118 mutation by assaying for expression levels. Specifically, the reference teaches that it is difficult to measure ERCC1 protein levels "because the experiments undertaken to define ERCC1 protein expression using immunohistochemical techniques were not judged reliably enough." Also, methods which assay for ERCC1 mRNA levels are unpredictable because the mRNA "can be quantified only in fresh tumors that are handled in conditions allowing high-quality RNA isolation to perform quantitative reverse transcription-PCR."

The unpredictability of assaying for alternative genotypes as indicative of response to treatment is supported by the teachings of Yu (Cancer Letters. 2000. 151: 127-132). Yu (2000) reported that the ERCC1 mRNA levels are correlated with clinical resistance to platinum-based therapy in ovarian cancer and gastric carcinoma (page 128, col. 1). The reference teaches that in human gliomas, a change in ERCC1 copy number is frequently observed. However, Yu (page 131) found that ERCC1 allelic loss or gain is not associated with response to cisplatin treatment, and thereby does not appear to account for the change in ERCC1 mRNA levels in cancer patients sensitive or resistant to cisplatin therapy.

Additionally, Britten (International Journal of Cancer. 2000. 89: 453-457) teaches that ERCC1 protein levels are not correlated with cisplatin resistance in cervical tumors. Britten concludes that the association between ERCC1 mRNA levels and cancer may

be an epiphenomenom, i.e., "mRNA levels may be a surrogate marker for some other determinant of response to chemotherapy in these cells" (see page 456).

It is also unpredictable as to whether samples other than intratumoral colorectal cancer samples can be analyzed for the presence of the codon 118 C to T polymorphism as indicative of survival following 5-FU/oxiplatin therapy. The specification (page 35) teaches only the results of a study obtained using intratumoral samples. It is well known in the art that mutations arise spontaneously in tumor samples, such that a polymorphism present in normal tissue may not be present in a tumor tissue and vice versa. Since it is the tumor itself that responds to the treatment, the presence or absence of a the polymorphism in non-tumor tissue does not predict the occurrence the same polymorphism in cancer tissue or the response of a patient to chemotherapy. The specification does not provide any data on the presence of the ERCC1 codon 118 polymorphism in normal tissue and response of a patient to 5-FU/oxiplatin therapy or any other therapy.

Amount of Direction or Guidance Provided by the Specification and Degree of Experimentation:

The specification does not provide sufficient guidance as to how to extrapolate the findings regarding the ERCC1 C/C codon 118 genotype and response to 5-FU/oxaliplatin treatment to other types of treatment. Extensive experimentation would be required to identify other combinations of fluoropyrimidines and platinum compounds which are correlated with the occurrence of the ERCC1 C/C genotype. The outcome of such experimentation cannot be predicted and is thus considered to be undue.

While methods for sequencing nucleic acids are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for polymorphisms that may linked to a particular phenotype, such as response to chemotherapy. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional combinations of drugs that are correlated with the C/C genotype.

Additionally, the specification does not provide sufficient guidance as to how to practice a method wherein a polymorphism or genotype is indirectly assayed for by, for example, detecting an allele that is in linkage disequilibrium with the codon 118 polymorphism or any other polymorphism. The specification does not identify any specific polymorphisms that are in linkage disequilibrium with codon 118 polymorphism and which are correlated with response to therapy. The specification also does not provide sufficient guidance as to how to perform any type of activity assay to indirectly detect the presence of the codon 118 polymorphism or any polymorphism or genotype in any other gene.

The specification does not provide sufficient guidance to enable the skilled artisan to extrapolate the findings obtained with survival response following 5-FU/oxiplatin treatment in patients having metastatic colon cancer to other outcomes following other types of treatment. The specification does not provide a clear structure-function relationship between the codon 118 polymorphism and response to therapy that would allow one to predictably extrapolate the findings obtained with 5-FU/oxiplatin

therapy to other therapies. As stated in the specification (page 36) "(a) search of the literature failed to provide an explanation of how a "silent" polymorphism that results in a codon of lesser usage can be associated with higher levels of mRNA. Without being bound by any theory, Applicants note that this polymorphism is associated with ERCC1 mRNA levels and therefore can predict survival of patients with metastatic colorectal cancer treated with 5-FU/oxaliplatin."

Working Examples:

The specification provides a working example in which a correlation between the presence of the C/C genotype and survival in metastatic colorectal cancer patients following treatment with 5-FU/oxiplatin.

No working examples are provided in which the presence of the codon 118 ERCC1 mutation is correlated with response to other types of treatment or is correlated to other clinical outcomes following treatment.

No working examples are provided in which the codon 118 ERCC1 polymorphism is specifically indirectly detected by assaying for an alternative polymorphism/mutation or by performing a biological activity assay.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement

provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification has not enabled one of skill the art to practice the invention as it is broadly claimed because the specification does not teach an association between the ERCC1 codon 118 C/C genotype and response to a representative number of different types of fluoropyrimidine and platinum combination therapy. Further, the specification does not provide sufficient guidance as to how to indirectly detect the C/C genotype in order to select a therapy or determine a patient's likelihood of longer survival following therapy. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Response to Remarks

In the response, Applicants traverse this rejection by stating that there is a link between members of the drug classes of fluoropyrimidines and platinum compounds in their chemical structures and mechanisms of action. Applicants point to Papamicheal as teaching equivalents of 5-FU, including prodrugs, analogs and derivatives. It is stated that oxaliplatin is in the same family as cisplatin and carboplatin and that platinum-

based drugs act by cross-linking to DNA and disrupting DNA synthesis, transcription and function. Wiseman et al is cited in support of this argument. Applicants conclude that the ERCC1 polymorphism at codon 118 can predict responsiveness to therapy comprising any fluoropyrimidine and any platinum drug.

These arguments have been fully considered but are not persuasive. Applicants have established only an association between response to 5-FU/oxaliplatin combination therapy and the presence of the C/C genotype at codon 118 of the ERCC1 gene, but not an association between the genotype at codon 118 and response to any combination of fluoropyrimidine and platinum drugs. The cited art of Wiseman and Papamichael fail to provide any evidence that a representative number of distinct fluoropyrimidine and platinum drugs have a similar mechanism of action that is effected by the presence of the C/C genotype. In fact, the cited references are silent with respect to the effect of the C/C genotype and response to fluoropyrimidine and platinum combination therapy. The fact that other fluoropyrimidines and platinum drugs exist and have been used to treat metastatic colon cancer is not persuasive to overcome the present grounds of rejection since it remains highly unpredictable as to which, if any, additional combinations of fluoropyrimidines and platinum drugs, are correlated with the C/C genotype. As set forth in the above rejection, the specification does not provide a clear structure-function relationship between the codon 118 polymorphism and response to therapy that would allow one to predictably extrapolate the findings obtained with 5-FU/oxiplatin therapy to other therapies. The specification (page 36) teaches that a "search of the literature failed to provide an explanation of how a "silent"

polymorphism that results in a codon of lesser usage can be associated with higher levels of mRNA. Without being bound by any theory, Applicants note that this polymorphism is associated with ERCC1 mRNA levels and therefore can predict survival of patients with metastatic colorectal cancer treated with 5-FU/oxaliplatin." Applicants have not established how the silent polymorphisms effects response to 5-FU/oxaliplatin combination therapy, so that one could predictably extrapolate the findings obtained with 5-FU/oxaliplatin to any other fluoropyrimidine compound and any other platinum compound.

Additionally, it is noted that Papamichael teaches that 5-FU is characterized by marked schedule dependency in both the quality and quantity of its effects (page 480). Papamichael teaches that fluoropyrimidines have different mechanisms of activity and different degrees of effectiveness. For example, the fluoropyrimidine doxifluridine must have its ribosyl group removed by the enzyme uridine phosphorylase to produce 5-FU (pag482, col. 1, 2nd full para). Papamichael teaches that this enzyme is reported to be more activity in some tumor cells than in normal tissues, resulting in an improved ratio in tumor bearing mice, but that very high activity is found in normal human liver casting doubt on doxyfluridine's claimed sensitivity. Thereby, the results obtained with 5-FU cannot be extrapolated to all fluoropyrimidine drugs because it has not been established that 5-FU derivatives, such as doxifluridine, will also alter a patient's sensitivity to therapy based on the presence or absence of the ERCC1 codon 118 genotype.

Applicants state that Hirschhorn does not evaluate ERRC1 polymorphisms and response to cancer treatment. This argument is not persuasive because Hirschhorn was

not cited for such teachings. Rather, Hirschhorn was cited as establishing the unpredictability in the art of establishing an association between a polymorphism and a phenotype. Hirschhorn teaches that this art in general is unpredictable, stating that "of the 166 putative associations studied three or more times, only 6 have been consistently replicated" (see abstract).

Applicants state that Winter applies only to a mutation in Exon 1. It is asserted that Winter does not apply to the present claims which are now limited to the mutation at codon 118 in exon 4. However, Winter was cited as teaching that while the mutation in exon 1 of ERCC1 has been previously disclosed as being associated with ERCC1 mRNA levels (page 2110), Winter found that the variant and wildtype ERCC1 transcripts were present at similar ratios in the tissues examined. Winter (page 211s) also teaches that the alternatively spliced transcript is present in both normal and cancer cells and does not appear to be related to the occurrence of cancer. Thereby, Winter establishes the unpredictability in determining the effect of a polymorphism on mRNA levels, and the association of such polymorphisms to a phenotype. Since the present claims do not specify the methodology by which the genotype at codon 118 is determined, the present claims include methods of indirectly assaying for the codon 118 genotype, such as methods which detect ERCC1 mRNA levels. Thereby, the teachings of Winter are in fact relevant to the claims as amended.

Applicants state that the teachings of Yu and Kang are directed to predicting response to ovarian cancer treatment and that the present claims are limited to methods of treating metastatic cancer. However, the findings of Yu and Kang establish the

unpredictability in the art of extrapolating the findings of the ERCC1 codon 118 mutation to treatment with any fluoropyrimidine and platinum compounds. In particular, Yu (1997) found that the 118 AAT and AAC codons were present in both ovarian cancer tissues that were sensitive to cisplatin treatment and in ovarian cancer tissues that were resistant to cisplatin treatment. Yu did not observe an association between the occurrence of the C/C, C/T or T/T genotypes and response to cisplatin in ovarian cancer patients. Kang (2006) teaches that there was no significant association observed between the ERCC1 codon 118 polymorphism and overall survival in ovarian cancer patients treated with platinum-based drugs (see abstract and page 323). Further, Kang states that, as of 2006, the mechanism by which the ERCC1 polymorphism effects response to chemotherapy remains unclear. It is stated that "functional data supporting the association between the ERCC1 polymorphism and its activity are still controversial and insufficient" (page 323). Thus, Kang clearly teaches that in the absence of information regarding the mechanism of effect of a polymorphism, one cannot predict how that polymorphism will effect responsiveness to chemotherapy.

Applicants asset that the teachings of Lee, Viguier (2005), Yu (2000), and Britten are not relevant to the claims as amended. Applicants state that the claims are not directed to evaluating gene expression or protein levels of ERCC1. However, the present claims recite only a step of screening for a genotype at codon 118 of the ERCC1 gene. The claims do not recite any particular process steps or means for screening for the genotype. The specification also teaches that the codon 118 genotype is correlated with ERCC1 mRNA levels. Accordingly, in the absence of any recitation in

the claims as to the methodology or means for detecting the codon 118 genotype, it appears that the claims are in fact inclusive of methods of indirectly detecting the genotype by assaying for mRNA or protein levels.

Regarding the Viguier reference, Applicants stat that Viguier did not measure survival time following therapy and therefore not Applicants' endpoint. Applicants conclude that the results reported in Viguier are not within the scope of the amended claims. However, claims 1, 4, and 16-18 are directed to methods of selecting therapy. The fact that Viguier did not measure survival time following therapy is not relevant to these claims since these claims are not directed to methods of determining a patient's survival time following therapy. Also, Viguier did study the sensitivity of patients carrying the codon 118 polymorphism to therapy, as determined by a reduction in tumor load or progression of cancer. The responsiveness of a patient to therapy is in fact relevant to the selection of therapy and is predictive of the patient's long term survival. That is, if a patient's tumor does not respond to treatment, it is highly unlikely that the patient will have a longer survival as compared to a patient that does respond to treatment. Further, Viguier does in fact support the finding of the high level of unpredictability in extrapolating the results obtained with the codon 118 polymorphism to response to other chemotherapies. Viguier teaches that while the codon 118 T/T genotype was associated with response of metastatic colorectal cancer patients to 5-FU/oxiplatin, the T/T, C/T and C/C genotypes were not associated with response to 5-FU alone or 5-FU in combination with irinotecan (page 6215). The reference (page 6216) teaches that the lack of association between the ERCC1 polymorphism and response to 5-FU therapy "is

not surprising because ERCC1 is unlikely to play a role in the repair of 5-FU-induced lesions." Given that Applicant's have not established a clear structure—function relationship between the codon 118 genotype and response to or long term survival following any combination of a fluoropyrimidine and platinum drug, the findings of Viguier are in fact relevant to the claimed invention.

Moreover, Viguier (page 6216) teaches the unpredictability of indirectly assaying for the codon 118 mutation by assaying for expression levels. Specifically, the reference teaches that it is difficult to measure ERCC1 protein levels "because the experiments undertaken to define ERCC1 protein expression using immunohistochemical techniques were not judged reliably enough." Also, methods which assay for ERCC1 mRNA levels are unpredictable because the mRNA "can be quantified only in fresh tumors that are handled in conditions allowing high-quality RNA isolation to perform quantitative reverse transcription-PCR."

The response traverses the rejection as it applies to the lack of enablement of assaying any biological sample for a codon 118 genotype. Applicants cite Shen as teaching that the C to T polymorphism at codon 118 can be found in normal, healthy individuals at a frequency of 0.46. However, Shen does not teach the existence of the C to T polymorphism at codon 118 in subjects having metastatic colon cancer and the correlation between the occurrence of this polymorphism in non-colon cancer cells and response to therapy or longer survival. As set forth in the above rejection, the specification (page 35) teaches only the results of a study obtained using intratumoral samples. It is well known in the art that mutations arise spontaneously in tumor

samples, such that a polymorphism present in normal tissue may not be present in a tumor tissue and vice versa. Since it is the tumor itself that responds to the treatment, the presence or absence of a the polymorphism in non-tumor tissue does not predict the occurrence the same polymorphism in cancer tissue or the response of a patient to chemotherapy. The specification does not provide any data on the presence of the ERCC1 codon 118 polymorphism in normal tissue and response of a patient to 5-FU/oxiplatin therapy or any other therapy. Also, regarding newly added claims 24-28, the specification has not established that the presence of the T allele in, for example, buccal or saliva samples, would be indicative of a subject less likely to have a longer survival. Given that the mutations arise spontaneously during the occurrence of cancer, a patient with a T/C genotype in a buccal or saliva sample, may have a C/C allele in colon tumor tissue samples. Therefore, the genotype of such samples would not be predictive of response to therapy or long term survival following therapy.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4, and 16-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/173,889. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '889 are both inclusive of methods for selecting a therapeutic regimen for treating cancer comprising screening a cell or tissue sample from a patient for a genomic polymorphism or genotype. While the claims of '889 do not specifically recite the detection of the codon 118 C to T polymorphism in ERCC1, when read in light of the specification of '889, it is clear that the broad recitation of any polymorphism or genotype is intended to encompass the codon 118 C to T polymorphism in the ERCC1 gene (see, e.g., para [0279] and [0280] of '889). Further, while the claims of '889 do not recite that the treatment is treatment of metastatic colon cancer with 5-FU and oxaliplatin, when read in light of the specification of '889, it is clear that the broad recitation of any treatment for any cancer is inclusive of treatment of metastatic colon cancer with 5-FU and oxaliplatin. Regarding claims 19-28, while the claims of '889 do not recite predicting a patient's longer survival based on the presence of the codon 118 genotype, the claims of '889 do encompass selecting a patient for therapy based on the presence or absence of the C/C genotype. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the

methods of '889 so as to have also predicted the likelihood of longer survival following 5-FU/oxaliplatin therapy based on the presence of the codon 118 genotype since patients specifically selected for this therapy based on a positive clinical response to the therapy would have been expected to have had a longer survival following therapy.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks

In the response, Applicants "defer responding to the provisional grounds of these rejections until allowable subject matter has been indicated." While it is noted that Applicants defer responding to the rejection, the rejection is maintained and made final for the reasons set forth above.

New Grounds of Rejection

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19-28 are indefinite over the recitations of "longer survival." The term "longer" is a relative term which renders the claim indefinite. The term "longer" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of

the scope of the invention. The claims do not set forth what the survival time is being compared to and therefore it is unclear as to what constitutes longer survival. Similarly, claims 24-28 are also indefinite over the recitation of "less likely." The claims do not set forth what the likelihood is being compared to and therefore it is unclear as to what is intended to be encompassed by "less likely to experience longer survival."

Priority

6. The claims are entitled to priority only to PCT/US03/24065, filed July 31, 2003. The claims are not entitled to priority to provisional applications 60/400,276, 60/400,250 or 60/400,249 because these applications do not provide support for the presently claimed invention. It is noted that the 60/400,253 application, filed 7/13/02 discloses a method of obtaining a nucleic acid sample from intratumoral tissue of a subject having metastatic colorectal cancer and assaying the nucleic acid sample to determine the identity of the nucleotides in codon 118 to thereby detect the presence of codon AAC or AAT (e.g., page 2 and 25). The '253 application also provides support for the concept that the codon 118 C/C genotype is associated with associated with survival following 5-FU/oxaliplatin treatment, wherein patients having the C/C genotype survived for 531 days, patients with the C/T genotype survived for 254 days, and patients with the T/T genotype survived for 256 days (page 25). It is stated that the codon 118 polymorphism "maybe able to predict survival in patients with metastatic colorectal cancer treatment with 5-FU/oxaliplatin" (page 26). However, the '253 application does not provide support for the broader concepts encompassed by the claims of selecting a therapy comprising any combination of a fluoropyrimidine and platinum compound, or predicting likelihood

or less likelihood of longer survival following treatment with any combination of a fluoropyrimidine and platinum compound, treatment with any fluoropyrimidine and platinum compound together with radiation therapy, assaying for the codon 118 ERCC1 genotype by assaying any biological sample, and indirectly assaying for the codon 118 ERCC1 genotype using any methodology or means to infer the presence of the codon 118 ERCC1 genotype. It is noted that a claim as a whole is assigned an effective filing date, rather than the subject matter within a claim being assigned individual effective filing dates. Accordingly, the present claims are entitled only to the filing date of July 31, 2003.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 16-22, and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (Proceedings of the American Association for Cancer Research. March 2002. 43: 321, Abstract 1519 (cited in the IDS of May 15, 2008).

Park teaches a method of detecting the presence of the C or T polymorphism at codon 118 of the ERCC1 gene in intratumoral tissue samples from human subjects having metastatic colorectal cancer and treated with 5-FU/oxalipaltin. Park teaches that increased ERCC1 mRNA levels are directly related to clinical resistance to platinum chemotherapy. Park also teaches that the absence of the ERCC-1 C allele was associated with higher ERCC1 mRNA levels. The authors conclude that the codon 118 polymorphism "may potentially have a role [in] the prediction of clinical outcome in patients with metastatic colorectal cancer treated with 5-FU/oxaliplatin."

Park does not specifically exemplify a method of selecting a patient for therapy with 5-FU/oxaliplatin by assaying for the presence of the C/C genotype at codon 118 or predicting likelihood of longer survival by assaying for the presence of the C/C genotype at codon 118.

However, given the teachings of Park that increased ERCC1 mRNA levels are associated with resistance to treatment, and thereby with poorer response to treatment, and the teachings of Park that the C/C genotype is associated with decreased ERCC1 mRNA levels (while the T/T and C/T genotypes are associated with increased ERCC1 mRNA levels), and in view of the specific teachings of Park that the codon 118 polymorphism may be predictive of clinical outcome in metastatic colorectal cancer patients treated with 5-FU/oxaliplatin, it would have been obvious to one of ordinary skill

in the art at the time the invention was made to have applied the findings of Park to a method for selecting patients for 5-FU/oxaliplatin therapy and for predicting longer survival following 5-FU/oxaliplatin therapy. One would have been motivated to do so since Park teaches that the C/C genotype could be detected as indicative of susceptibility to 5-FU/oxaliplatin therapy, and thus longer survival following said therapy. Thereby, application of the method of Park to the selection of patients for 5-FU/oxaliplatin therapy and for predicting a patient's likelihood of longer survival following this therapy would have provided the expected benefit of ensuring the selection of the most effective therapy for patients having metastatic colorectal cancer.

8. Claims 4, 23 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al in view of Culy (Drugs. October 2000. 60(4): 895-924).

The teachings of Park are presented above. Park does not teach that the patients selected to receive 5-FU/oxaliplatin therapy or predicted to have longer survival following 5-FU/oxaliplatin therapy are also treated with radiation therapy.

However, Culy teaches that it was conventional in the art at the time the invention was made to also treat cancer patients, and particularly metastatic colorectal cancer patients, receiving 5–FU/oxaliplatin therapy with radiation therapy (page 905, and Tables III and IV).

In view of the teachings of Culy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Park so as to have also selected patients for 5-FU/oxaliplatin therapy that further received radiation therapy and to have predicted the likelihood of survival of patients having 5-

FU/oxaliplatin therapy and also receiving radiation therapy, since additional treatment of metastatic colorectal cancer with radiation therapy was conventional in the art at the time the invention was made and was known to further enhance the effectiveness of chemotherapy.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634